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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,421	10/05/2000	Sundarasamy Mahalingam	UPAP-0350	1903

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	24

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/485,421	Applicant(s) MAHALINGAM ET AL.
	Examiner Q. Janice Li	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *20 February 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/29/03 has been entered.

The amendment filed on 1/29/03 has been entered as Paper #23. Claims 1 and 7 have been amended. Claims 1-11 are pending in the application and under current examination.

The previous objection and rejections that do not reiterated in this Office action are withdrawn. The arguments in paper #23 would be addressed to the extent that applies to the current rejection.

Priority

This is a 371 filing of U.S. patent application, which claims the benefit of priority to U.S. provisional application 60/055,754. However, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Objections

Claim 7 is objected to because of the following informalities: the amended claim 7 recites an amino acid sequence 56-84, which differs from the previous version, "amino acid sequence 59-84", and the change has not been marked. It is unclear whether this is an inadvertent error or an intentional amendment. Appropriate clarification is required.

Specification

The specification is objected to because this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "a therapeutic compound", dependent claims 2-4 refer to the compound as "said therapeutic compound", whereas depend claims 5 and 6 refer to the compound as "said compound". It is suggested that the claims be amended to be consistent when refer to the same compound.

Claim 7 is vague and indefinite because the use of the word "either". This is because the word "and" should not combined with "either". Moreover, the word "either" appears to serve as a conjunction in the phrase beginning in line 3, and the phrase linked by "either" is "amino acid sequence 56-84", however, it is unclear which protein the amino acid sequence belongs to, and thus, the claim is ambiguous.

Claim 7 is vague and indefinite because of the claim recitation, "a compound" (line 1), "a conjugated compound" (line 2), "said compound" (line 2), and "said conjugated compound" (line 6), it is unclear whether the compound in conjugated and unconjugated form is the same compound, and because "said compound" could refer to either "a compound" or "a conjugated compound", the claim as written is ambiguous.

Claims 8-11 are vague and indefinite because of the claim recitation, "said compound". Claims depend from claim 7, claim 7 encompasses an unconjugated compound and a conjugated compound, it is unclear which compound "said compound" refers to, and thus, the claims are ambiguous.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, and 7-9 are rejected under 35 U.S.C. 102(e) as being anticipated by *Cohen et al* (USP 6,043,081).

Claim 1 is drawn to a composition comprising a nuclear localization sequence fragment of HIV-1 Vpr (instant SEQ ID No. 1) comprising amino acid sequence 17-36 and/or amino acid sequence 56-84 conjugated to a therapeutic compound. Claims 7-9 are drawn to a method of using the composition for delivering a compound to a cell, wherein the compound is a plasmid DNA molecule.

Cohen et al teach a chemeric molecule (composition) comprising a HIV-1 vpr protein or fragment thereof, covalently attached to a therapeutic molecule (compound), wherein the molecule is a therapeutic protein or a DNA construct (column 5, lines 7-10, 41-48, and column 9, lines 15-22). *Cohen et al* also teach that carboxyl terminal of the Vpr is important for nuclear localization and that Vpr could be a protein that function as

a transport polypeptide for biological targeting in a non-viral specific manner (column 3, lines 13-45). In claim 11 of the cited art, the targeting element of the vector is a fragment of HIV-1 Vpr comprising amino acids 1-72, 1-88, or 1-93 which encompassing amino acid sequence 17-36 and/or amino acid sequence 56-84. In SEQ ID No. 4, the fragment of HIV-1 Vpr comprises amino acid sequence 17-36. Therefore, *Cohen et al* anticipate the instant claims.

Claims 1, 5-11 stand rejected under 35 U.S.C. 102(b) as being anticipated by *WO9608970*.

In paper #23, Applicants argue that claim 1 as amended recites "a nuclear localization sequence fragment of HIV-1 Vpr comprising amino acid sequence 17-36 and/or amino acid sequence 56-84", nowhere does the *Weiner* reference teach such a fragment of Vpr, nor does the Weiner reference teach the nuclear localization sequences of Vpr.

The argument has been carefully considered but found not persuasive for reasons of record set forth in the correspondent sections of Papers 11, 15, and 17, and following.

First, given the broadest reasonable interpretation, the claims as written, encompass any composition containing any fragment(s) of HIV-1 Vpr protein having amino acid sequence 17-36 and/or amino acid sequence 56-84; claims as written also encompass the full length HIV-1 Vpr, because the open language, "comprising" embraces additional sequence elements, thus, claim 1 does not place any limitation on

the amino acid as long as it comprises the recited fragments of HIV-1 vpr. Second, regarding the fragment, *WO9608970* teaches, in page 36, lines 29-30, that nucleic acid molecules are conjugated to "a Vpr protein or its fragment", here, the "fragment" embraces any vpr fragment of less than 95 amino acid residues, and embraces fragments that inherently have the recited sequence fragment(s) of claim 1. Third, *WO9608970* clearly teaches, in page 36, lines 24-32, that agents whose presence in the nucleus is desirable may be conjugated to vpr or fragments thereof. Here, *Weiner et al* clearly teach the nuclear localization property of Vpr. Fourth, newly added claim recitation, "a nuclear localization sequence" is a phrase defining the function of the fragment of HIV-1 vpr, whereas the novelty of the invention is determined by the structure of the amino acids claimed. MPEP 2112.01 teaches, "PRODUCTS OF IDENTICAL CHEMICAL COMPOSITION CAN NOT HAVE MUTUALLY EXCLUSIVE PROPERTIES.' A CHEMICAL COMPOSITION AND ITS PROPERTIES ARE INSEPARABLE". THEREFORE, IF THE PRIOR ART TEACHES THE IDENTICAL CHEMICAL STRUCTURE, THE PROPERTIES APPLICANT DISCLOSES AND/OR CLAIMS ARE NECESSARILY PRESENT. *IN RE* SPADA, 911 F.2D 705, 15 USPQ2D 1655, 1658 (FED. CIR. 1990).

Applicants further argue that the list of the Vpr fragments in Weiner reference is not sufficiently limited or well delineated and the Weiner reference teaches a genus, whereas instant applicants claim a subgenus or a part of another genus.

The argument has been fully considered but found not persuasive. The list of fragments in page 53 of *Weiner et al* is an illustrative, non-limiting embodiment, and the claims as written are claiming the same genus as taught by *Weiner et al*. This is because the skilled artisan cannot make a distinction between the instantly claimed genus and the genus taught by *Weiner et al* from either the structure or the function of

the vpr protein or fragments thereof as discussed in the immediate preceding paragraph. Therefore, the composition taught by *Weiner et al* encompasses that of instant claims 1 and 7, and *WO9608970* anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cohen et al* (USP 6,043,081), in view of *Katz et al* (US 6,005,004) and *Zuckermann et al* (US 6,468,986).

These claims are drawn to a composition comprising a nuclear localization sequence fragment of HIV-1 vpr conjugated to a therapeutic compound, wherein the compound is a nucleic acid molecule such as a plasmid, or an antisense oligonucleotide, wherein the vpr fragment further comprising a polycationic amino acid sequence, and the nucleic acid is conjugated to the vpr fragment by ionic bonds. *Cohen*

et al fails to teach a polycationic amino acid sequence in the composition or an antisense oligonucleotide as the therapeutic compound, and fails to teach the ionic bonds between the polycationic molecule and the nucleic acid.

Katz et al teach to selectively transport therapeutic materials to brain cells using lipophilic-polycationic delivery systems comprising a biologically active molecule covalently bonded with cationic carriers and permeabilizer peptides to enhance efficiency for drug delivery to neuronal cells (see abstract). They teach that the biologically active molecules include polypeptides, nucleic acids, antisense oligonucleotides, and transfection vectors (see column 2, lines 3-6, and claims 1-5). They go on to teach that noncovalent bonding could also be employed if the strength is comparable to the covalent bond (column 23, lines 54-55). *Zuckermann et al* teach a gene delivery system comprises polycationic agent complexed with a nucleic acid vector (claims 1 and 2) via noncovalent bonding, such as hydrogen bonds and/or ionic bonds (column 29, lines 50-54), *Zuckermann et al* teach that the use of such polycationic agents will increase the frequency of uptaking polynucleotides, condensing, and protecting polynucleotides from serum and nuclease degradation during the delivery process (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of *Cohen et al*, by simply including a polycationic molecule to the vpr conjugated composition in the delivery of any known therapeutic compound, such as antisense oligos, and using any known chemical bonding means as taught by *Katz et al* and *Zuckermann et al* with a reasonable

expectation of success. The ordinary skilled artisan would have been motivated to do so because it was known that the addition of the polycationic molecule would enhance intracellular penetration of the therapeutic compound and reduce the degradation of nucleic acids during the delivery process. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over *WO9608970*, and further in view of *Katz et al* (US 6,005,004) and *Zuckermann et al* (US 6,232,295).

Please note that this rejection is a modification of the previous rejection "as being unpatentable over *WO9608970*, and further in view of *Katz et al* and *Kayyem et al*". The rejection has been modified because *Katz et al* teach the noncovalent bonding that encompasses the ionic bonds, but it is *Zuckermann et al,* who clearly teaches the ionic bonding between the polycationic agent and a nucleic acid, thus, *Kayyem* reference has been replaced by *Zuckermann* reference. However, the previous rejection based on the combined teachings of *WO9608970* and *Katz et al* still applies to current rejection.

In paper No. 23, Applicants argue, in addition to attacking the *WO9608970* reference, that neither *Katz* reference nor the *Kayyem* reference teaches the fragments of claim 1. Applicants further argue that it is only through hindsight reconstruction that the Examiner is able to make the claimed invention by combining the references cited.

The argument has been carefully considered but found not persuasive for reasons of record and following.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the *Weiner* reference clearly teaches the nuclear localization property of HIV-1 Vpr and fragments thereof, the *Katz* reference teaches selectively transporting therapeutic material into cells using polycationic delivery systems. The *Zuckermann* reference teaches a gene delivery system comprises polycationic agents complexed with a nucleic acid vector by ionic bounds, *Zuckermann et al* teach that such polycationic agents will increase the frequency of uptake polynucleotides, condensing, and protecting polynucleotides from serum and nuclease degradation during cell delivery process (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of *WO9608970*, by simply including a polycationic peptide sequence to the vpr conjugated composition to further enhance intracellular delivery of nucleic acids as taught by *Katz et al* and *Zuckermann et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because it is known that the addition of the polycationic molecule would enhance intracellular penetration and reduce the degradation of nucleic acids during the delivery process. Thus, the claimed invention as a whole was *prima facie* obvious.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

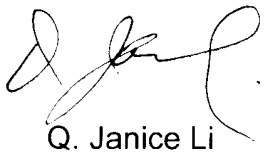
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Examiner
Art Unit 1632

QJL
April 21, 2003